713.01, page 700-164, column 1, fourth full paragraph. During the interview the rejections under 35 U.S.C. § 112, first paragraph were discussed. The subject matter discussed in the interview is set forth below.

In regard to the informalities in the drawings, Applicant is preparing and will submit formal drawings similar to those published in U.S. Pat No. 6,027,933 in a separate paper. Applicant respectfully requests that amendments changing the recited subparts of the figures to capital letters be deferred until that time, as the number of subparts for several of the figures will likely change.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7, and 77 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification does not adequately describe a method by which a heteromeric receptor is expressed on the surface of a cell.

Applicant maintains for the reasons of record that the specification enables expression of a fusion protein with the protein product of gene VIII on the surface of a procaryotic cell. The Examiner has not identified any deficiency in the guidance provided in the specification. Rather, the Examiner has alleged that there is no evidence of record that pVIII has ever been expressed on the surface of a cell by employing those techniques that were available to an artisan on 28 September 1990.

Applicant has previously provided Marvin et al. as evidence supporting the teaching in the specification that a fusion protein with the protein product of gene VIII (pVIII) can be expressed on the surface of a procaryotic cell. As acknowledged in the Office Action, Figure 1 of Marvin et al. "clearly shows that pVIII is expressed in the periplasmic membrane." Applicant has provided evidence that expression in the periplasmic membrane is understood in the art to be expression on the surface of a cell. Specifically, Alberts et al., as acknowledged in the Office Action, describes the MCP receptor proteins as periplasmic receptor proteins. Alberts et al. also identifies these periplasmically localized MCP receptor proteins as "cell surface receptors" on page 759, lines 24-31, as previously set forth on the record.

Further evidence that expression in the periplasmic membrane is understood in the art to be expression on the surface of a cell is demonstrated by Milligan and Koshland, J. Biol. Chem. 268: 19991-19997 (1993), provided as Exhibit A, and Falke and Koshland Science 237:1596-1600 (1987), provided as Exhibit B. Milligan and Koshland refer to the periplasmically located aspartate receptor of *S. typhimurium* as a cell surface in stating that

> in order to facilitate biochemical studies of cell surface receptors, a plasmid allowing expression of the periplasmic domain of the aspartate receptor from *Salmonella*

> *typhimurium* as a soluble periplasmic protein has been constructed.

Abstract, lines 1-5. Falke and Koshland also refer to the periplasmic aspartate receptor as a being on the surface of *E. coli* and *S. typhimurium* cells in stating that

> the aspartate receptor of *Escherichia coli* and *Salmonella typhimurium* is a cell surface sensory transducer that binds extracellular aspartate and sends a transmembrane signal to the inside of the bacterium.

Abstract, lines 1-4. Thus, a protein localized to the periplasmic membrane, such as the protein product of gene VIII shown in Figure 1 of Marvin et al. was understood in the art to be expressed on the surface of a cell.

Moreover, the assertion on page 3, lines 6-9 of the Office Action, that an identification of the MCP proteins as cell surface receptors by Alberts et al. would not be accepted, is unfounded. Applicant respectfully submits that the textbook of Dr. Bruce Alberts and his co-authors, Dr. Dennis Bray, Dr. Julian Lewis, Dr. Martin Raff, Dr. Keith Roberts and Dr. James Watson, has been widely accepted by those skilled in the art and there is no substantive evidence to the contrary. Thus, as corroborated by the evidence of record, the guidance provided in the specification including, for example, the methods taught for expression of a heteromeric receptor at the inner membrane of a procaryotic cell, would have been understood by those skilled in the art to yield a surface expressed heteromeric receptor.

Applicant respectfully disagrees with the assertion in the Office Action that the phage shown in Figure 1 of Marvin et al. is not attached to the surface of the cell for the purposes of the instant invention. The specification teaches that the claimed composition can be used for a variety of purposes and in a variety of methods. Applicant acknowledges that the claimed compositions can be used, for example, in a method of isolating a cell. The specification teaches that receptors that are on the surface of cells can be screened using standard affinity procedures such as affinity chromatography, solid phase blotting procedures or the panning procedures of Parmley and Smith, Gene 73:305-318 (see, for example, page 12, line 29, through page 13, line 8 of the specification). Parmley and Smith describe on page 314, in the paragraph spanning columns 1 and 2, that cells can be transferred to 96 well microtiter plates in a method called micropanning and that since micropanning is performed on individual clones, there is little doubt that colonies in a positive spot represent antibody reactive phage and they can be propagated directly for further analysis. In view of the teaching and guidance provided in the specification and that which was known in the art, those skilled in the art would have recognized that even if a heteromeric receptor that is on the surface of a cell is identified by a binding interaction and later extruded, a screen such as the micropanning procedure can be used to identify and isolate the heteromeric receptor and the cell from which it is produced.

Regarding phage which become attached to a cell during infection as shown in Figure 1 of Marvin et al., Applicant

respectfully submits that those skilled in the art would have recognized that such cells are not encompassed by the claims because the claims recite polypeptides being expressed as a fusion protein with the protein product of gene VIII of filamentous bacteriophage on the surface of the cell. Those skilled in the art would have recognized that a fusion protein on the surface of a cell due to an infecting phage is not expressed by that cell.

Claims 1-4, 7, 16-19, 21-29, 31, 32, 66-75, and 77 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the disclosure does not enable expression of functional portions of any heteromeric receptor proteins, other than the variable heavy and variable light chains of immunoglobulins, on the surface of filamentous bacteriophage.

Applicant respectfully traverses the rejection. Applicant respectfully disagrees with the assertion in the Office Action that immunoglobulins are not structurally and functionally representative of the genus of proteins encompassed by the term heteromeric receptor. Applicant maintains for the reasons of record that, in view of the teaching and guidance provided in the specification, immunoglobulins would have been understood to be representative of the genus of heteromeric receptors. In this regard, the evidence of record including the definitions for the term receptor in Webster's Collegiate Dictionary and Stenesh's Dictionary of Biochemistry and Molecular Biology, demonstrates that immunoglobulins were understood by those skilled in the art to be representative of heteromeric receptors.

Furthermore, neither Nakanishi nor any of the art of record supports the Examiner's exclusion of antibodies, or fragments thereof, from being encompassed by the term heteromeric receptor. The Examiner has not pointed to any description in Nakanishi that excludes immunoglobulins from being heteromeric receptors. The description in Nakanishi et al. pointed to by the Examiner merely describes ligand gated ion channels as having 5 subunits and 4 transmembrane domains in each subunit. The assertion on page 5, lines 2-7 of the Office Action, that immunoglobulins and T-cell receptors that are members of the immunoglobulin superfamily are not functionally and structurally representative of the genus of proteins encompassed by the limitation heteromeric receptor, is not factually supported. Rather the assertion appears to be based on the personal knowledge of the Examiner and is contrary to the evidence of record. Therefore, absent evidence supporting the rejection or an affidavit pursuant to 37 C.F.R. § 1.104 (d)(2) supporting the Examiner's assertion, the rejection is unfounded.

Applicant respectfully points out that, in contrast to the assertion on page 5, lines 11-13, of the Office Action, no argument was ever made stating that "'transmitter receptors' are functionally excluded from the limitation 'heteromeric receptor.'" Rather, Applicant asserted on page 11, lines 15-22 of the response mailed January 29, 2001 that:

> As set forth previously, Applicant does not claim all forms of heteromeric receptors. Instead, the claims are directed to only those first and second polypeptides which

> form functional heteromeric receptors. Thus, the claims do not encompass an integral membrane polypeptide expressed on the surface of a filamentous phage <u>if they would not assemble to a functional heteromeric receptor as described and claimed</u>. (Emphasis added)

Thus, only those transmitter receptors that would not assemble to a functional heteromeric receptor as described and claimed fall outside of the scope of the claims according to the previous arguments. Applicant respectfully submits that the arguments of record are consistent with the teachings of the instant application.

<u>Rejections under 35 U.S.C. § 112, second paragraph</u>

Claims 70 and 75 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite for reciting the phrase "has substantially the same sequence."

Applicant respectfully traverses the rejection. Applicant maintains, for the reasons of record, that in view of the teaching and guidance provided in the specification, one skilled in the art will be able to identify a sequence as being substantially similar to a sequence recited in the claims.

> The fact that claim language, including terms of degree, may not be precise does not automatically render the claim indefinite under 35 U.S.C. § 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packaging, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim

> language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.

MPEP 2173.05(b), pg 2100-196 column 2, first full paragraph. Furthermore, the use the term "substantially" has been accepted in patent examination and upheld by the courts.

> The term "substantially" is often used in conjunction with another term to describe a particular characteristic of the claimed invention. It is a broad term. *In re Nehrenberg*, 280 F.2d 161, 126 USPQ 383 (CCPA 1960)... The court held that the limitation "which produces substantially equal E and H plane illumination patterns" was definite because one of ordinary skill in the art would know what was meant by substantially equal. Andrew Corp. v. Gabriel Electronics, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988).

MPEP 2173.05(b), pg 2100-197, column 2, last paragraph.

As set forth previously on the record, the specification provides teaching and guidance regarding the structure and function of the claimed vectors and regarding minor modifications of the vector that yield substantially the same sequence. In view of the guidance and teaching in the specification and that which was known in the art for direct comparison of a biological sequence to a reference sequence, at both a structural and functional level, one skilled in the art would have been able to identify a sequence as substantially the same as a sequence recited in the claims. Thus, the subject matter of claims 70 and 75 are sufficiently clear. Accordingly,

Applicant requests that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Double-patenting rejection

Claims 1-5, 7 and 16-33 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-32 of U.S. Patent Number 5,871,974. In making the rejection, the Office Action alleges that the pending claims are encompassed by the Patent claims and relies upon *Eli Lilly and Co. v. Barr Labs, Inc.* 222 F.3d 973, 55 USPQ2d 1609 (Fed. Cir. 2000) in alleging that in relation to an obviousness-type double patenting rejection, a species is obvious in view of the genus encompassing it.

Applicant respectfully traverses the rejection and maintains that pending claims 1-5, 7 and 16-33 are not obvious over claims 1-32 of U.S. Patent No. 5,871,974, because the plurality of cells recited in claims 1-5 and 7, are directed to the species "procaryotic cells" whereas the claims of the cited patent are directed to the genus "cells" and a genus does not, on its face, render obvious one of many particular species. Applicant respectfully submits that the rejection is unfounded because the decision relied upon in the Office Action has been vacated by an *en banc* ruling of the Federal Circuit Court.

> Acting *en banc*, the court vacated the panel's original opinion entered on August 9, 2000, which is reported at 222 F.3d 973, 55 USPQ2d 1609 (Fed. Cir. 2000). The *en banc* court

> reassigned the opinion to the panel for a specific revision of the double patenting section. . . The panel's original judgement, which reversed the district court's determination that claim 7 of U.S. Patent No. 4,626,549 ("the '549 patent") is not invalid for double patenting, is reaffirmed, but on a different legal basis.

(emphasis added) *Eli Lilly and Co. v. Barr Labs, Inc.* 251 F3.d 955, 958, 58 USPQ2d 1865 (Fed. Cir. 2001). For the Examiner's convenience a copy of *Eli Lilly and Co. v. Barr Labs, Inc.* 251 F3.d 955 (Fed. Cir. 2001), is attached herewith as Exhibit C.

As shown in Exhibit C, the legal basis upon which the *en banc* court decided invalidity for obviousness-type double patenting is non-analogous to the instant application. The legal basis upon which invalidity for double patenting was confirmed rested in part upon the conclusion that

> Our case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.

(emphasis added) 251 F3.d 955, 971. However, nowhere does the *en banc* court, in vacating its earlier decision, support an obviousness-type double patenting rejection of later species claims over earlier genus claims. Therefore, the final ruling of the court does not support the rejection of the pending claims, which recite the species "procaryotic cells," over the claims of the '974 patent, which recite the genus "cells." Accordingly, Applicant requests that rejection of claims 1-5, 7 and 16-33,

under the judicially created doctrine of obviousness-type double patenting, be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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